Insight in the brain

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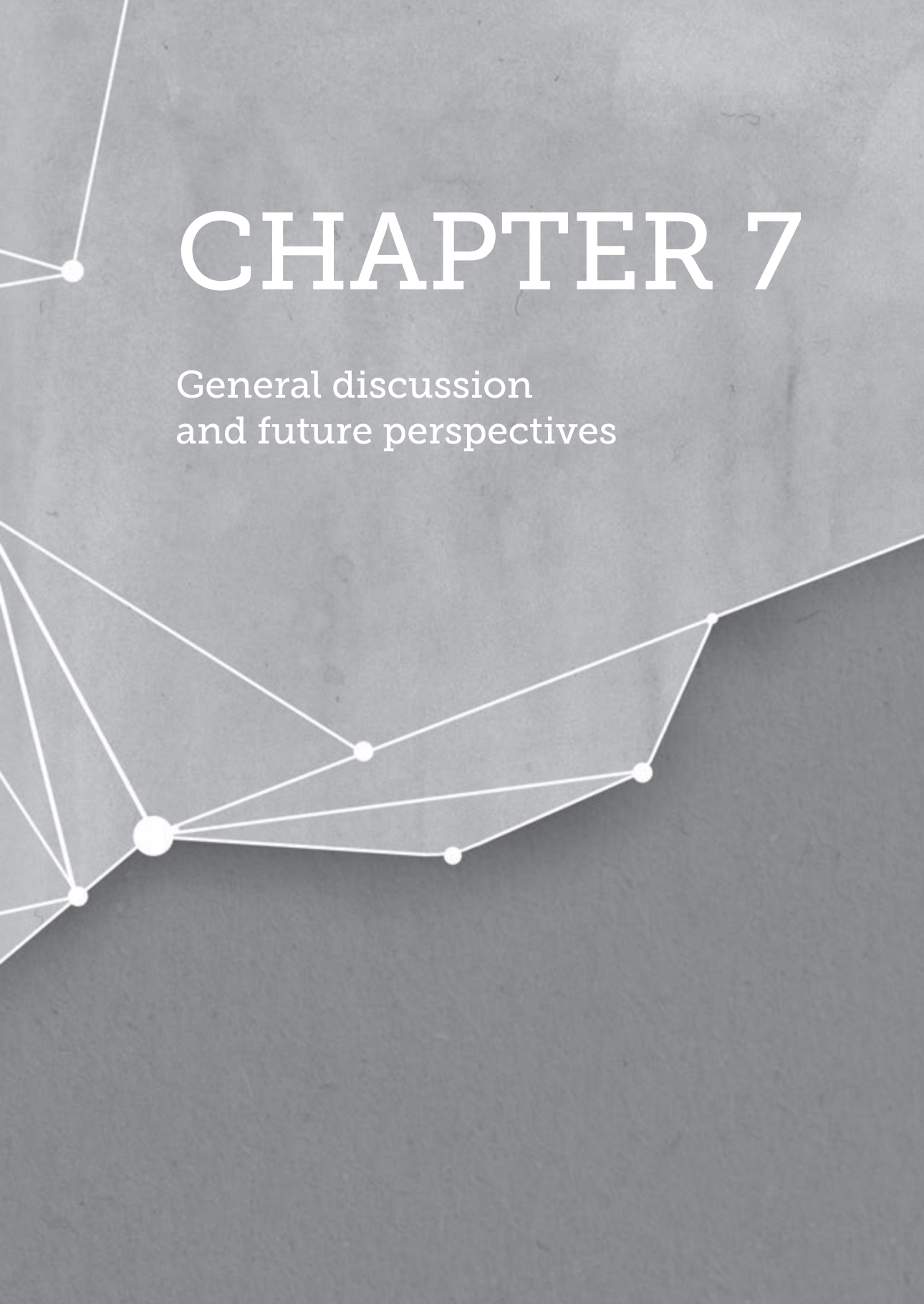
CHAPTER 7

General discussion and future perspectives



The main aim of this thesis was to increase knowledge on the structural and functional neural substrates of insight in patients with a psychotic disorder. Our focus was on brain connectivity given that the parallelly distributed patterns of activation of brain networks (i.e. neural synchrony) are thought to underpin complex mental abilities. In Chapters 2-5, we focused on *clinical insight* in patients with a psychotic disorder. However, patients might admit to being ill and needing treatment without a real understanding of their illness and integration of their illness in their self-concept. Therefore, in Chapters 2 and 4-6, we additionally studied a second type of insight called *cognitive* insight. This involves individuals' attributive metacognitive ability (i.e. awareness and understanding of one's own thought processes), and directly measures distorted thinking styles. Learning more about brain regions underlying these (distorted) thinking styles increases knowledge that could be of clinical significance, as these cognitive styles might be targeted in treatment. In the current chapter, main findings are summarized and integrated, and critical considerations and future perspectives are discussed.

7.1 Clinical insight

7.1.1 Global brain abnormalities

The meta-analyses and systematic review of the literature that are described in **Chapter 2,** suggest spatially diffuse global abnormalities across the brain in patients with impaired insight, given that structural and functional abnormalities of numerous regions across the brain were associated with poorer clinical insight. Indeed, two meta-analyses on either voxel-based morphometry (VBM)-studies or functional magnetic resonance imaging (fMRI)-studies did *not* reveal a clear structural or functional substrate of clinical insight by pinpointing specific isolated brain areas. This might suggest that the literature is plagued by false positive findings. However, a lot of these regions were consistently found across studies. Moreover, on the global level, three meta-analyses including studies on either i) the sum of total gray and white matter volume, ii) total gray matter volume, or iii) total white matter volume, showed that patients with poorer clinical insight have both lower total gray and white matter volume. All in all, this suggests that methods taking the complex network of the whole brain into account may provide a more meaningful explanation of impaired insight in psychotic disorders than a focal (regional) approach. To this end, connectivity at the systems-level was investigated in Chapter 5.

In **Chapter 5**, we found converging evidence for abnormalities at the *systems-level* in poorer clinical insight in patients with a psychotic disorder. In this chapter, gray matter connectomes were created based on similarity of gray matter structure, and clinical

insight was related to several brain organization indices. We found lower clustering coefficient, reflective of less segregation into subnetworks and a more random brain topology, in patients with lower scores on one dimension of clinical insight, namely the ability to attribute symptoms to the illness (i.e. SAI-E Relabeling of symptoms). Additionally, we showed that higher betweenness centrality, indicative of an increase in hub characteristics, was also related to clinical insight (i.e. PANSS G12 scores). On a more speculative note, it has been suggested that a failure of performance of hub-regions (i.e. regions that are important for communication across the brain as they are well-connected to other regions) in schizophrenia leads to a compensatory reorganization with a shift and increase of hub-characteristics to brain areas that are less central. This could be reflected in an average increase in hub-characteristics, and might have global influence on complex higher-order functions underlying insight. A previous study indeed found reduced centrality of conventional hub-regions (i.e. dorsolateral prefrontal, insula, anterior cingulate cortex) and emergence of peripheral hubs (i.e. fusiform gyrus) in schizophrenia (Palaniyappan et al., 2019). The study described in Chapter 5 is the first study creating gray matter connectomes at the individual level, allowing the investigation of the relationship between gray matter brain organization indices and symptoms. Altogether, our results indicate that system's level gray matter brain organization indices are related to inter-individual differences in insight into psychosis. In this thesis, we did not investigate the relation between clinical insight and *functional and DTI connectivity* at the systems-level. One could expect, however, that these systems-level abnormalities would also be reflected in the functional and DTI connectome. Future studies could shed more light on this matter.

7.1.2 Processes underlying clinical insight

Our findings in Chapter 2 and 5 support the idea that clinical insight might require several basic as well as higher-order cognitive functions (e.g. social-, neuro-, and metacognitive functions such as self-reflectiveness, perspective taking, cognitive flexibility and self-referential processing), that cannot be pinpointed to isolated brain regions as they require global brain integration.

Good clinical insight has been suggested to require adequate integration of externally- and internally-generated information to integrate information from the environment into one's self-representation (Ebisch and Aleman, 2016). This is consistent with the model as described by Lysaker et al. (Lysaker et al., 2018). Lysaker and colleagues suggest that good insight requires the ability to construct and continuously update a currently correct account of one's own state while integrating information on internal states, the external circumstances and perspectives of others. The authors suggest

that these abilities might be affected by basic biological processes or structures, impaired perspective taking and sense of self as well as by one's own experiences and more general socio-political factors.

Cognitive neuroscience models that attempt to explain impaired insight also stress the necessity of intact metacognitive and sensory abilities (e.g. self-evaluation and reflection) for good insight (Flashman and Roth, 2004). In order to have good clinical insight, one should be able to create an accurate meta-representation of oneself which requires adequate metacognitive abilities (Bergé et al., 2011). Altogether, our findings indeed suggest that complex processes, that require global brain integration, underlie insight.

7.1.3 Local abnormalities and processes underlying clinical insight

Current treatment options have limited success in the improvement of insight (Pijnenborg et al., 2013b). Studies that shed light on specific brain regions that are involved in insight are important for treatment development, as they may yield clues about underlying functional processes, whereas information at the most macroscopic level might not be helpful. Moreover, global abnormalities might be driven by local abnormalities. In Chapter 5, no significant associations were found between poorer insight and local *gray matter* network properties. Therefore, in Chapters 2-4, we studied the relationship between insight and local *white matter and functional* connectivity.

The systematic review in **Chapter 2** showed that the inferior frontal gyrus/ventrolateral prefrontal cortex was most consistently implicated in clinical insight in studies examining brain structure as well as brain activation. The inferior frontal gyrus has been implicated in the inhibition of one's own perspective (Van der Meer et al., 2011), while the ventrolateral prefrontal cortex has been suggested to play a role in cognitive control and selective attention for salient stimuli (Wearne, 2018). The ventrolateral prefrontal cortex has been shown to coactivate with other regions within the salience network (e.g. insula) and the central executive network (e.g. dorsolateral prefrontal cortex) (Wearne, 2018). Two meta-analyses, described in Chapter 2, that integrated studies conducted on left or right frontal gyrus volume revealed significant positive relationships with insight. As these studies pointed towards an important role of the frontal gyri in poorer insight, we aimed to investigate *frontal* white matter and functional connectivity in Chapters 3 and 4.

In **Chapter 3**, we investigated how clinical insight relates to abnormalities in *local white matter* as measured with Proton Magnetic Resonance Spectroscopy (^{1}H-MRS). We found that there were lower N-acetylaspartate (NAA) concentrations in the white

matter of the left (dorsolateral) prefrontal cortex of patients with lower insight (as measured with the Birchwood Insight Scale (BIS)). This correlation was driven by the awareness of illness dimension. Reduced NAA concentrations are thought to indicate reduced neuronal integrity which might be caused by impaired functioning of axons causing abnormal neural connectivity (Du et al., 2013; Tang et al., 2007). Thus, findings in this chapter pointed towards *local white matter* prefrontal dysconnectivity in patients with impaired clinical insight.

These findings are in line with several previous studies that showed volumetric (Shad et al., 2006b, 2006a, 2004), as well as functional- and DTI connectivity abnormalities of the prefrontal cortex in patients with poorer clinical insight (Ćurčić-Blake et al., 2015; Liemburg et al., 2012). This might be explained by the role of the dorsolateral prefrontal cortex in executive functions such as the abilities to monitor and evaluate one's own behavior and to adjust one's own thoughts and beliefs to changing situations (Shad et al., 2007, 2006b) as well as metacognitive functions such as the abilities to make complex representation of oneself and others, to reflect upon oneself and to take the perspective of others. Altogether, in this study we confirm and extend results of prior studies that implicated prefrontal white matter abnormalities in poorer clinical insight by showing that these abnormalities are also reflected in NAA-concentrations.

In **Chapter 4**, we aimed to study how local *functional* connectivity abnormalities relate to clinical insight. An fMRI emotion regulation task was used to probe an emotion regulation network including prefrontal areas given that (1) the prefrontal cortex plays a critical role in emotion generation and regulation (Dixon et al., 2017), (2) numerous studies have shown emotional dysregulation in schizophrenia (Henry et al., 2007; Horan et al., 2013; Morris et al., 2012; Perry et al., 2012; Van der Meer et al., 2014), and (3) good insight might require intact emotion regulation abilities to deal with the negative emotions accompanying awareness of illness. Therefore, we investigated how clinical insight relates to activation and connectivity during emotion regulation. Connectivity was measured with generalized psychophysiological interactions (gPPI) yielding information on task-dependent connectivity. We found lower activation of areas involved in cognitive-emotional control (i.e. left striatum, thalamus and insula, right insula and caudate, and right pre- and postcentral gyrus) and visual processing of negative stimuli (i.e. left superior occipital gyrus and cuneus, and the right middle and superior occipital gyrus and cuneus) in patients with a lower ability to relabel symptoms (i.e. SAI-E Relabeling of symptoms). Additionally, we found higher connectivity between the midline medial frontal gyrus, an important area for execution of emotion regulation (Kohn et al., 2014; Vanderhasselt et al., 2013), and the right middle occipital gyrus in patients with poorer clinical insight (i.e. PANSS G12 scores).

A previous study found lower connectivity between the right posterior insula and pre- and postcentral gyri in schizophrenia patients with lower insight (i.e. PANSS G12 scores) (Chen et al., 2016). The authors suggested that decreased connectivity between the insula and sensorimotor areas (i.e. pre-and post-central gyrus and occipital areas) in patients with impaired insight might be explained by abnormal integration of somatosensory and visual signals, leading to abnormalities in self-other distinction (Chen et al., 2016). The ability to discriminate oneself from others is essential for insight. The systematic review in **Chapter 2** also revealed that insular (in addition to inferior frontal) abnormalities were found most frequently in fMRI-activation studies. Various studies implicated the importance of the insula in insight (Palaniyappan et al., 2011; Sapara et al., 2015; Shad and Keshavan, 2015; van der Meer et al., 2013) and stressed its role in self-monitoring (Sapara et al., 2015) and other introspective processes (Palaniyappan et al., 2011). The insula has been shown to be involved in "being in touch with oneself" in a quite literal way as it is involved in the representation of awareness of bodily states (Damasio, 1999). The insula also plays an important role in the Salience Network, mediating the switch between interoceptive and exteroceptive attention (Menon and Uddin, 2010). Abnormalities of the salience network have been previously implicated in poorer clinical insight (Gerretsen et al., 2014). Our findings in Chapter 3 could be explained such as that individuals with poorer ability to relabel symptoms might direct their attention less inward to monitor their expressions (Hayes et al., 2010; Richards and Gross, 2000). This explanation could be in line with the denial model, which suggests that poor insight is caused by the use of denial as a coping strategy in order to reduce distress caused by stigma associated with diagnosis of schizophrenia (Cooke et al., 2005). However, more objective evidence for the denial model is needed. An alternative explanation could be that somatosensory and visual signals are abnormally integrated in patients with poorer ability to relabel symptoms, giving rise to problems in self-other distinction and insight.

In **Chapter 4**, we additionally found less activation of areas involved in visual processing of negative stimuli, which could indicate attentional shifts and an implicit reduction in processing of emotion-evoking aspects of negative stimuli during expressive suppression. This might be explained by the decoupling hypothesis that suggests that when the mind wanders, attention decouples from perception (Schooler et al., 2011; Smallwood and Schooler, 2006). Attention might thus be relocated to task-unrelated thoughts resulting in superficial processing of perceptual information. This implicates important roles for the DMN, salience or attention networks, as well as networks involved in processing of perceptual information in impaired insight. The systematic review in **Chapter 2** indeed revealed that fMRI-connectivity studies most frequently implicated the Default Mode Network. The DMN consists of medial and lateral parietal,

medial prefrontal, and medial and lateral temporal brain areas (Raichle, 2015). The function of the DMN is less well-understood but it has been suggested to be involved in introspective cognitive functions including mind-wandering (Christoff et al., 2009; Mason et al., 2007).

Summarized, abnormalities in the interplay between networks such as the DMN, attention networks and (somatosensory) perception networks might interrupt processes necessary for good insight, such as switching between interoceptive and exteroceptive attention and integrating external information into one's self-concept. An overview of all findings related to clinical insight in this thesis can be seen in Figure 1.

Chapter	Brain structure			Brain function	
	Local	Connectivity	Global	Local	Connectivity
2	▼**Gray matter volume frontal gyrus** Volume inferior and middle frontal gyrus, inferior and superior temporal gyrus		▼**Gray matter volume** ▼**White matter volume**	**Not significant** Activation inferior frontal gyrus and insula	Connectivity Default Mode Network
3		▼NAA white matter dorsolateral prefrontal cortex **BIS Total* **BIS Awareness of illness*			
4				▼Activation insula, caudate, right pre- and postcentral gyrus, middle and superior occipital gyrus, and cuneus **SAI-E Relabeling of symptoms*	▲Connectivity between midline medial frontal gyrus and middle occipital gyrus **SAI-E Subtotal*
5	Not significant		▼Clustering coefficient gray matter connectome **SAI-E Relabeling of symptoms* ▲Betweenness centrality gray matter connectome **PANSS G12*		

Figure 1: *Overview of findings on clinical insight.*
NB: results of meta-analyses are shown in **bold** text in Chapter 2, review results in regular text.

7.1.4 Distinct processes underlying different dimensions of insight

An important question is which brain regions and connectivity patterns underlie the distinct dimensions of clinical insight. At the global (i.e. whole brain) level, our findings in Chapter 5 demonstrate that relabeling of symptoms is associated with lower segregation of gray matter connectomes. No significant associations were found between global brain organization indices and other clinical insight dimensions. Compared to the other dimensions of clinical insight, relabeling of symptoms appears to be of higher-order as it not only requires illness awareness but also the ability to integrate self-related information with information concerning the social and cultural environment while actively processing ongoing information from oneself as well as others. These processes might represent an interplay of more dynamic and higher-order processing which might be more severely affected by disturbances at the systems-level rather than regional abnormalities. Additionally, lower clustering coefficient suggests less segregated specialized processing of information, which might affect higher-order processes (such as relabeling of symptoms) more than basic processes.

Locally, awareness of illness was found to be related to dorsolateral prefrontal cortex abnormalities. This is in line with a study of Shad and colleagues that suggested that dorsolateral prefrontal cortex abnormalities may underlie impaired awareness of illness by interfering with self-monitoring (Shad et al., 2006a). In the empirical chapters, no relationships were found with the Need for treatment dimension. This is line with earlier studies, that rarely found significant associations between this dimension and brain structure (i.e. only two studies) (Buchy et al., 2011; Sapara et al., 2007). Recognizing the need for treatment might be associated more with environmental and personal factors such as stigma sensitivity, support from family and friends, and culture. One study, for example, showed that insight into the need for treatment was influenced by frequency of interactions between the patient and their parent (Macgregor et al., 2015). The systematic review and meta-analyses in Chapter 2 did *not* reveal different local neural correlates underlying distinct insight dimensions, however, given that regions were usually involved in more than one dimension of insight. A few regions were only associated with one dimension of insight, but this was not consistently found across multiple (i.e. >1) studies. Altogether, it remains unclear whether clinical insight dimensions depend on different brain regions, but global integration deficiencies likely underlie complex insight dimensions such as relabeling of symptoms.

7.1.5 Proposed model to explain poor clinical insight

Based on the results in this thesis, we propose a new model of brain areas and processes underlying poor clinical insight. We suggest that awareness of symptoms requires intact functioning of the dorsolateral prefrontal cortex, as it requires executive

functions such as the abilities to monitor and evaluate one's own behavior and to adjust one's own thoughts and beliefs to changing situations (Shad et al., 2007, 2006b). Relabeling of symptoms requires complex cognitive functions (e.g. social-, neuro-, and metacognitive functions such as self-reflectiveness, perspective taking, cognitive flexibility and self-referential processing), that cannot be pinpointed to isolated brain regions as they require global brain integration. We hypothesize that need for treatment cannot be pinpointed to neural abnormalities, but that it might be associated more with environmental and personal factors.

7.2 Cognitive insight

The construct of clinical insight is complex and our findings suggest that abnormalities across the brain give rise to difficulties in several complex processes that are necessary for having good insight. These findings raise the question whether directly measuring patients' attributive metacognitive ability or cognitive style might yield more clinically relevant information. After all, these cognitive styles can be directly targeted in treatment. Therefore, in this thesis, we also extensively studied the neural correlates of cognitive insight.

7.2.1 Brain abnormalities underlying poor cognitive insight

In **Chapter 2**, a systematic review of the literature revealed that structural neuroimaging studies most often found hippocampal involvement, while fMRI-studies most often found involvement of the inferior frontal gyrus/ventrolateral prefrontal cortex in cognitive insight in patients with a psychotic disorder. It should be noted, however, that studies that found hippocampal involvement were all ROI-studies that specifically focused on that region. Our findings in **Chapter 4**, were not in line with other literature, as we showed lower activation of brain systems subserving control and execution of emotion regulation (i.e. left and right pre- and postcentral gyrus and the left middle cingulate gyrus) in patients with lower self-reflectiveness. A speculative explanation of our results could be that that patients with lower self-reflectiveness (i.e. lower cognitive insight) are less involved in emotion regulation because of an implicit reduction of processing of emotion-evoking aspects of negative stimuli. This might be in line with the denial model, which suggests that poor insight is caused by the use of denial as a coping strategy in order to reduce distress caused by stigma associated with diagnosis of schizophrenia (Cooke et al., 2005).

Our findings of lower path length, clustering coefficient and small-world coefficients of gray matter connectomes in patients with poorer cognitive insight, as described in **Chapter 5,** show support of disturbances at the systems-level. Lower clustering and

small-world coefficients suggest a global imbalance between functional integration and segregation which may lead to dysfunction (Rubinov and Sporns, 2010). The association with general cognitive insight appeared to be driven by the self-certainty dimension, while no significant associations were found for the self-reflectiveness dimension. Additionally, locally, we found lower clustering and small-world coefficient of the left inferior occipital gyrus in patients with lower cognitive insight suggesting that this region might drive system-level abnormalities.

As we established *local as well as systems-level abnormalities* in poorer cognitive insight in patients in Chapters 4 and 5, we aimed to get a more comprehensive view of the neural substrate of cognitive insight by combining data from different MRI-modalities in **Chapter 6**. This chapter only included data of healthy individuals as cognitive insight reflects general cognitive styles that do not necessarily pertain illness. We hypothesized that cognitive insight is a dynamic process and therefore related it to temporal dynamics of resting state functional connectivity. Additionally, we related cognitive insight to characterizations of *structural* (i.e. DTI and gray matter structure) networks. Our findings in Chapter 6 suggest less stable functional and structural networks in individuals with poorer cognitive insight, and specifically poorer self-reflectiveness, with an overly present DMN. That is based on our findings that individuals with lower cognitive insight switched more between states, and spent less time in a globally synchronized state. An explanation for our results that individuals with lower cognitive insight spend less time in the globally synchronized baseline state, could be that in these individuals the transition towards specialized networks is more difficult, rendering more frequent switching between states and less stable functional networks. With regard to the self-reflectiveness dimension, individuals with lower self-reflectiveness also switched more between states and spent less time in a globally synchronized state (at trend-level significance). Additionally, they spent more time in, had a higher probability of, and had a higher chance of switching to a state entailing Default Mode Network (DMN) areas. *Thus, an overly present DMN appears to play a key role in poorer self-reflectiveness*. The DMN has been suggested to be involved in introspective cognitive functions including mind-wandering (Christoff et al., 2009; Mason et al., 2007). With lower self-reflectiveness, DTI-connectomes were segregated less (i.e. lower clustering coefficient), and there was a higher connectedness of the left angular gyrus (i.e. lower path length). The left angular gyrus has shown to be a key region in the DMN (Greicius et al., 2003; Raichle et al., 2001; Uddin et al., 2009). Lower clustering coefficients of DTI-connectomes were significantly related to higher switching frequency and a higher probability of occurrence of the state similar to the DMN. Thus, less anatomical segregation into clearly-defined networks appears

to be related to less stable functional networks and spending more time in the DMN. Altogether, our results suggest that individuals with lower self-reflectiveness show structural over-connectedness of the angular gyrus, a key region of the DMN, and that this is associated with an overly present DMN. Summarized, findings in this chapter implicate less stable functional and structural networks, as well as an important role of the DMN in poorer cognitive insight. An overview of all results with regard to cognitive insight can be seen in Figure 2.

Chapter	Brain structure		Brain function		
	Local	Global	Local	Network	Global
2	Volume hippocampus		Activation inferior frontal gyrus/ ventrolateral prefrontal cortex		
4			▼Activation pre- and postcentral gyrus and left middle cingulate gyrus **Self-reflectiveness*		
5	▼Clustering coefficient gray matter connectome left inferior occipital gyrus **Composite index* ▼Small-world coefficient left inferior occipital gyrus **Composite index*	▼Clustering coefficient gray matter connectome **Composite index* **Self-certainty* ▼Path length gray matter connectome **Composite index* ▼Small-world coefficient gray matter connectome **Composite index* **Self-certainty*			
6	▼Path length DTI connectome left angular gyrus **Self-reflectiveness*	▼Clustering coefficient DTI connectome **Self-reflectiveness*		▲Lifetime DMN-state **Self-reflectiveness* ▲Probability of occurrence DMN-state **Self-reflectiveness* ▲Switching frequency VAN-DMN **Self-reflectiveness*	▲Switching frequency **Composite index* **Self-reflectiveness* ▼Lifetime global synchronization state **Composite index* **Self-reflectiveness*

Figure 2: *Overview of findings on cognitive insight.*

NB: chapter 6 only includes healthy individuals, whereas the other chapters include patients with a psychotic disorder and healthy controls.

7.2.2 Processes underlying cognitive insight

Findings in patients with a psychotic disorder show that system-level abnormalities in gray matter connectomes are related to cognitive insight, and self-certainty specifically. Locally, findings in this thesis implicated gray matter network abnormalities of the left inferior occipital gyrus in lower cognitive insight, and lower activation in the pre- and postcentral gyrus, and left middle cingulate gyrus in lower self-reflectiveness. These areas have not been implicated in cognitive insight in previous studies, however. The review of the literature in Chapter 2 implicated the inferior frontal gyrus/ventrolateral prefrontal cortex and hippocampus most frequently in poorer cognitive insight.

The ventrolateral prefrontal cortex has been linked to self-reflection, cognitive control of memory (Badre and Wagner, 2007; Levy and Wagner, 2011) and working memory (Buchy et al., 2015; Wolf et al., 2006). These memory processes have been linked to the ability to hold information online and are hypothesized to play a role in the ability to consider alternative hypotheses about one's own (possibly incorrect) beliefs (Orfei et al., 2013). The hippocampus was also found to play a role in self-related processes in previous studies (Schmitz and Johnson, 2006), forming a network with the dorsomedial and -lateral prefrontal cortex that facilitates cognitive control and monitoring of self-related decisions. The hippocampus also plays a role in several memory processes (Sheldon and Levine, 2018) that have been associated with cognitive insight (Davies et al., 2017), in particular declarative memory. Thus, results suggest that cognitive insight mainly relies on the ability to retrieve and integrate self-related information.

In healthy individuals, our results show converging evidence of less stable functional and structural networks in individuals with poorer cognitive insight, or self-reflectiveness specifically, with a key role of the DMN. Individuals with lower cognitive insight spend less time in the globally synchronized baseline state which may make the transition towards specialized networks more difficult, rendering more frequent switching between states, less stable functional networks and an overly present DMN. Less stable functional networks and an overly present DMN were related to less anatomical segregation of the DTI connectome into subnetworks. Additionally, an overly connected left angular gyrus within the DTI connectome was also related to an overly present DMN.

7.3 Critical considerations and future perspectives

Several factors complicate the investigation of the neural substrate of insight. At this point, some of these factors will be shortly discussed whereas other factors will be discussed in more detail in subsections below. First, all studies were cross-sectional. Therefore, no conclusions on causality can be drawn. Future studies of longitudinal design, that preferably also include individuals at ultra-high risk for psychosis, could provide more information on how insight relates to brain connectivity over time and how that relates to cognitive models of insight. Additionally, it is unclear whether we completely capture the concept of insight with cross-sectional investigations as it is not a fully static construct. Insight appears to have trait- as well as state-like properties, given that it is associated with cognitive deficits, brain structural abnormalities and education, but also with symptom severity and it improves with antipsychotic treatment (Wiffen et al., 2010). Longitudinal studies, for example using experience sampling methodology, could shed more light on this matter. Second, samples were heterogeneous with regard to illness duration, symptomatology, illness severity, use of antipsychotics and substance (ab-)use. These factors have differential effects on insight. For example, a meta-analysis showed that clinical insight improves after treatment with antipsychotics, but only in the early phase of the disorder (Pijnenborg et al., 2015). However, samples in this thesis were very similar to the general patient population making our results more generalizable. Future studies could, for example, follow individuals at ultra-high risk or drug-naïve individuals with first-episode psychosis longitudinally. A clinically homogenous sample could provide information that is not confounded by illness duration nor antipsychotic use. Third, insight is currently viewed in a linear manner, i.e. low insight is pathological while high insight is good. Contradictory findings in the literature show that impaired insight on the one hand may be associated with negative factors such as poorer prognosis and increased symptomatology, while on the other hand it has also been associated with lower depressive symptoms and higher quality of life (Wiffen et al., 2010). This could be explained when viewing symptoms with a non-linear inverted U-shape curve, as suggested by Northoff & Tumati (Northoff and Tumati, 2019). They argued that pathology is reflected by either too low or too high scores on a symptom scale, while average scores reflect healthy functioning. The same line of reasoning might be applicable to insight. Last, impaired insight is not unique for psychosis but is also seen in other neurological and psychiatric illnesses such as dementias, substance-related disorders, and obsessive-compulsive disorder (Dam, 2006; Goldstein et al., 2009; Mangone et al., 1991; Matsunaga et al., 2002). It is unclear whether the neural substrate of impaired insight is similar across these disorders. Studies examining insight across disorders might shed more light on this. Other critical considerations are discussed in more detail below.

7.3.1 Measurements of insight

Most frequently used measures of insight are the Schedule for the Assessment of Insight – Expanded (SAI-E), item 12 of the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS item G12) and the Scale to Assess Unawareness in Mental Disorder (SUMD) (Kay et al., 1987; Shad et al., 2006b). There is consensus in the field that insight is a multidimensional construct, and most insight measures therefore consist of several subscales or aim to capture several subdimensions within one score. Studies often report scores on these subdimensions as well as total scores. In this thesis, clinical insight was measured with the PANSS G12 item (Chapters 3 and 5), the Birchwood Insight Scale (BIS) (Chapter 3) and the SAI-E (Chapters 4 and 5). These instruments have all shown to be reliable and valid measures of insight.

The PANSS G12 item is a single-item measure but it aims to capture multiple dimensions of clinical insight. Correlations with other measures of clinical insight, such as the SAI, SAI-E and BIS have shown to be strong (Sanz et al., 1998). In this thesis, the PANSS G12 item was strongly correlated (in the expected direction) with other insight measures, such as the BIS total score ($r=-0.6$, $p<0.001$, $n=81$; Chapter 3), SAI-E awareness of illness ($r_s=-0.61$, $p<0.001$, $n=62$), SAI-E Relabeling of symptoms ($r_s=-0.62$, $p<0.001$, $n=62$), SAI-E Need for treatment ($r_s=-0.47$, $p<0.001$, $n=62$) and the SAI-E subtotal score ($r_s=-0.69$, $p<0.001$, $n=62$) (Chapter 5). The PANSS is a rating scale for assessing positive, negative and general psychopathology symptoms in schizophrenia. Item G12 measures lack of judgment and insight. It is scored by a trained interviewer (1=no impairment; 7=severe impairment). Examples of questions used to answer this item are 'Do you need treatment?' and 'Why are you in this mental institution?'. A disadvantage of this measure, is that it does not measure distinct dimensions separately, so potential associations between one insight dimension and neural correlates might be obscured by non-existing associations between the other dimensions and neural correlates. Therefore, we additionally measured insight with multi-dimensional measures.

The BIS (Chapter 3) is an 8-item self-rating questionnaire with a total score ranging from 0 to 12. It consists of three subscales measuring three dimensions of clinical insight, namely awareness of illness, ability to relabel symptoms and awareness of need for treatment. Advantages of this questionnaire are that it is a brief, easy-to-administer measure that can easily be incorporated as an additional measure in clinical trials and studies that do not focus on insight specifically. The accuracy of self-report measures has been questioned in schizophrenia, however, as it might be argued that individuals with poor insight require insight to report about their

own insight. Yet, clinician- or researcher-rated measures might be more biased and influenced by patients' cognitive and communicative abilities. Therefore, the BIS was administered in Chapter 3, in addition to a researcher-rated measure of insight (i.e. the PANSS G12).

The last insight measure used in this thesis, is the SAI-E (Chapter 4 and 5). This is a semi-structured interview consisting of three subscales: (1) awareness of illness, (2) relabeling of symptoms to the illness, and (3) need for treatment. It comes with several advantages. First, no medical jargon or labels are used but questions about the disorder are adjusted to the patients' own words and descriptions. Second, some of the items are rated by a trained interviewer (items 1-9), while some are rated by the patient's clinician (A-C). Disadvantages of this insight measure, compared to the SUMD, are that it does not measure insight in social consequences of the disorder, and that it does not distinguish between current and retrospective awareness and attribution. The SUMD consists of 74 items, among which six general items and four subscales each consisting of 17 items. The general items measure current and past awareness of mental disorder, awareness of medication effects, and awareness of social consequences of the disorder. With the subscales, current awareness and attribution, as well as retrospective awareness and attribution with regard to specific symptoms, such as anhedonia and flat affect, can be measured. An important disadvantage of this scale is its length, rendering it not always practically possible to include this questionnaire in studies. Moreover, it is thorough but also complex, making it difficult to administer in participants with cognitive slowing or cognitive abnormalities, which are common symptoms in schizophrenia. The scale can be shortened in different ways, rendering different variations of the scale. An option would be to only rate the general items, but this would render it less detailed compared to the SAI-E and BIS, for example. Thus, given the lengthiness and complexity of the SUMD, we chose to use other commonly used insight measures in this thesis.

In this thesis, cognitive insight was measured with the Beck Cognitive Insight Scale (BCIS) (Chapters 4-7). This is a 15-item self-report questionnaire that measures (1) self-reflectiveness, and (2) self-certainty (Beck and Warman, 2004). Advantages of this scale are that (1) it can be used in nonclinical as well as in different clinical populations allowing comparisons the spectrum of healthy individuals and disorders, and (2) self-report questionnaires in general avoid researcher/clinician-bias (Marks et al., 2000). Disadvantages are, first, that it has been argued that a reliable report on one's insight requires good insight. However, the initial validation study showed significant correlations between the BCIS composite index score and being aware of a mental disorder as measured with the SUMD (Amador et al., 1993), between the

self-reflectiveness subscale scores and being aware of delusions as measured with the SUMD, and between change in BCIS-scores and change in positive and negative symptoms (Beck et al., 2004). In this thesis, we also found significant correlations between SAI-E subtotal scores and BCIS self-certainty scores (r=-0.55; p=0.002; n=30, Chapter 4), between SAI-E Awareness of illness subscale scores and BCIS self-certainty subscale scores (r=-0.62; p_{FDR}<0.001, n=30, Chapter 4), SAI-E Awareness of illness and BCIS self-certainty (r_s=-0.25, p=0.047, n=62; Chapter 5), SAI-E Need for treatment and BCIS self-certainty (r_s= -0.30, p=0.018, n=62; Chapter 5), and PANSS G12 and BCIS composite index scores (r_s=-0.33, p=0.008, n=62; Chapter 5). Several other studies from other groups have also shown reliability and validity of the BCIS and that it can distinguish patients with psychosis from patients without psychosis and healthy individuals (Riggs et al., 2012). Additionally, several studies showed increased self-certainty (i.e. poorer cognitive insight) in individuals with at-risk mental state (Uchida et al., 2014) or at clinical high risk for psychosis (Kimhy et al., 2014). Thus, results of previous studies suggest that individuals can reliably rate their experiences (Riggs et al., 2012). A second disadvantage of the BCIS is that it is unclear whether general thoughts patterns, as measured with the BCIS, are similar to thought patterns related to an illness. Patients with schizophrenia, for example, might show aberrant thought patterns related to their illness but not related to general topics. A last disadvantage of insight measures in general, is that there is no measure of real behavior. Ideally, insight measures would not only include researcher-, clinician- and self-rated parts but also an objective measure of behavior. However, such a lengthy and complex insight measure might have low feasibility.

7.3.2 Multicausal integrated explanations of impaired insight

Multicausal integrated explanations of impaired insight appear more likely than monocausal explanations given the small to modest effect sizes (of associations between insight and these factors) that are found and the variation between patients. A more holistic approach, in which information from different levels is integrated, would be useful to shed more light on explanations of interindividual variability in insight. One example of such an approach is a multiscale neuroscience approach in which data at different scales (i.e., genetic, molecular, cellular and macroscale structural and functional connectivity) is integrated to better relate brain structure, function and behavior (van den Heuvel et al., 2019). Another example of such an approach is the levels of explanation approach suggested by Hugdahl & Sommer (Hugdahl and Sommer, 2018). In this model, insight as a symptom is viewed in a vertical manner, in order to integrate and explain insight across different levels. Insight appears to be caused by a complex interaction of factors from these different levels (i.e. impairments in cognition, brain structure/

function, stigma, symptoms etc.). Integration of information of the brain imaging level with information from the cultural (i.e. norms, beliefs and attitudes; e.g. stigma), clinical (i.e. diagnoses, symptoms, personality), cognitive (i.e. cognition, executive functions, meta-awareness, emotion regulation) and cellular levels (i.e. synapses and neurotransmitters; e.g. NAA, glutamate) might give a more comprehensive view of the etiology of impaired insight. Either way, it is necessary that neurobiological, psychological and cultural/social findings are better integrated to get a clearer picture of the etiology of insight.

7.4 Clinical implications

Given the multidimensionality and complexity of the insight construct, as well as various cognitive functions and brain areas that might underlie it, a single treatment approach is unlikely to be successful (Osatuke et al., 2008). Indeed, current treatment options have limited success in improvement of insight (Pijnenborg et al., 2013b). Clinical trials that specifically focused on the improvement of insight showed improved insight but still left it unclear which components of these treatments led to the improvement (Guo et al., 2010; Lalova et al., 2013; Pijnenborg et al., 2019). Thus, the identification of brain mechanisms underlying impaired insight is a first step towards the development of more effective treatment options to enhance impaired insight so that prognosis can be improved.

Interventions aiming to improve insight should address multiple dimensions of insight through a combination of neurocognitive, metacognitive and social cognitive as well as psychosocial approaches. Given our results of global brain integration underlying complex insight dimensions, the integration of new information into one's self-concept could be an important part of treatment. This is consistent with the suggestion of Lysaker et al. that patients with schizophrenia should be helped in the integration of complex and negative experiences into their adapted self-concept (Lysaker et al., 2018).

Additionally, findings in Chapter 5 show that functional and structural networks of healthy individuals with lower cognitive insight, and more specifically poorer self-reflectiveness, are less stable. If these results are replicated in patients, our findings could have practical implications as it could inform interventions that reinforce functional networks, such as neurofeedback. Additionally, mind-wandering could be reduced through mindfulness meditation training as that might improve focus and sustained attention according to previous studies (Mooneyham et al., 2016;

Mrazek et al., 2013; Zanesco et al., 2016). Such approaches, thus, might increase stability of task-specific networks, decrease time spend in the DMN and ultimately improve the self-reflection abilities of individuals with low levels of such abilities. Previous studies already showed improvements of insight after mindfulness-based interventions (Chien and Thompson, 2014; Wang et al., 2016; Yılmaz and Okanlı, 2018).

7.5 Conclusions

Findings in this thesis show converging evidence that impairments in clinical and cognitive insight are associated with structural and functional abnormalities in the brain. Impairments in one dimension of clinical insight, namely awareness of illness, appear to be associated with abnormalities of the dorsolateral prefrontal cortex. This might be explained by the role of the dorsolateral prefrontal cortex in executive functions (i.e. the abilities to monitor and evaluate one's own behavior and to adjust one's own thoughts and beliefs to changing situations) as well as metacognitive functions (i.e. the abilities to make complex representation of oneself and others, to reflect upon oneself and to take the perspective of others). Impairments in global brain integration appear to underlie another dimension of clinical insight, namely poorer ability to attribute symptoms to the illness, suggesting that this dimension of clinical insight requires an interplay of complex functions. The Default Mode Network, and networks involved in attention and perception might play an important role in this dimension of clinical insight. Cognitive insight in patients with a psychotic disorder appears to mainly rely on the underlying functions of the hippocampus and ventrolateral prefrontal cortex to retrieve and integrate self-related information. Lastly, our findings implicate less stable functional and structural networks in healthy individuals with lower cognitive insight with a key role of the Default Mode Network, which has been shown to be involved in mind wandering.